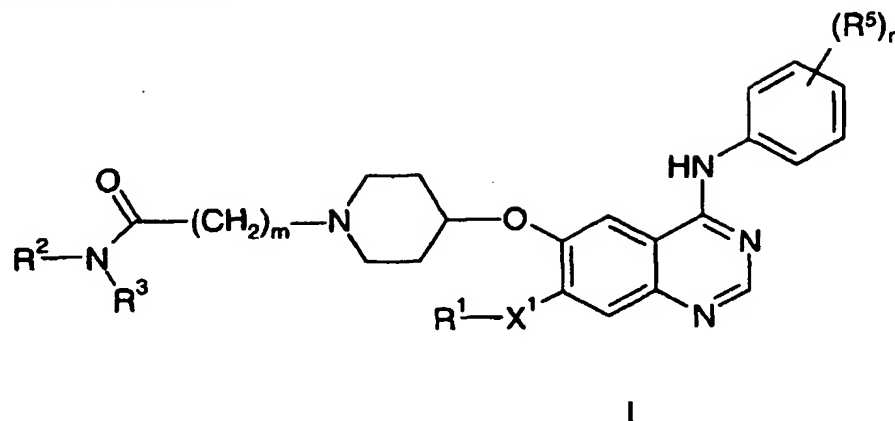


**CLAIMS**

1. A quinazoline derivative of the Formula I:



- 5 wherein  $n$  is 0, 1, 2 or 3,  
 each  $R^5$  is independently selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,  $N$ -(1-6C)alkylsulfamoyl, and  $N,N$ -di-[(1-6C)alkyl]sulfamoyl,  $C(O)NR^6R^7$  where  $R^6$  and  $R^7$  are independently selected from hydrogen, optionally substituted (1-6C)alkyl, optionally substituted (3-8C)cycloalkyl or optionally substituted aryl, or  $R^6$  and  $R^7$  together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring which may contain additional heteroatoms;
- 15  $X^1$  is a direct bond or O;  
 $R^1$  is selected from hydrogen and (1-6C)alkyl, wherein the (1-6C)alkyl group is optionally substituted by one or more substituents, which may be the same or different, selected from hydroxy and halogeno, and/or a substituent selected from amino, nitro, carboxy, cyano, halogeno, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl,  $N$ -(1-6C)alkylcarbamoyl,  $N,N$  di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,  $N$ -(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl, sulfamoyl,  $N$ -(1-6C)alkylsulfamoyl,  $N,N$ -di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and  $N$ -(1-6C)alkyl-(1-6C)alkanesulfonylamino;
- 25  $m$  is 0, 1, 2 or 3;

$R^2$  is hydrogen or (1-6C)alkyl; and

$R^3$  is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl or (1-6C)alkoxy, any of which can be optionally substituted on a carbon atom by a (1-6C)alkoxy, amino, (1-6C)alkylamino, di-(1-6C)alkylamino, or a group  $S(O)_s(1-6C)alkyl$  where  $s$  is 0, 1 or 2, or a saturated 5 or 6  
5 membered heterocyclic ring which optionally contains additional heteroatoms selected from oxygen, sulfur or  $NR^8$  where  $R^8$  is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylsulfonyl or (1-6C)alkylcarbonyl;

or  $R^2$  and  $R^3$  together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms selected from  
10 oxygen, S, SO or  $S(O)_2$  or  $NR^8$  where  $R^8$  is as defined above;  
provided that the quinazoline derivative is not:

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-  
15 oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonyl]-piperidin-4-yl-oxy}-quinazoline;

20 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(diethylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

25 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(pyrrolidin-1-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(4-methyl-piperazin-1-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-ethoxy-quinazoline;

30 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-(2-methoxy-ethoxy)-quinazoline;

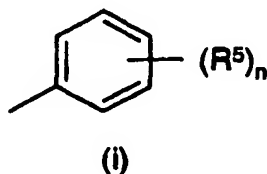
4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(ethylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(isopropylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 5 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonylmethyl]-piperidin-4-yl-oxy}-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylmethyl]-piperidin-4-yl-oxy}-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 10 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(methylamino)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 15 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(pyrrolidin-1-yl)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 20 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(methylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(2-methoxyethyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 25 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(3-methoxypropyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(N-methyl-N-3-methoxypropyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
- 30 4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline; or

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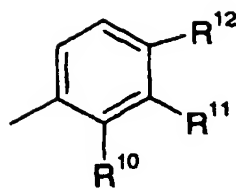
4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylpropyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;  
or a pharmaceutically acceptable salt thereof.

- 5 2. A quinazoline derivative according to claim 1, wherein n is 1, 2 or 3.
3. A quinazoline derivative according to claim 1 or claim 2, wherein n is 2 or 3.
4. A quinazoline derivative according to any one of claims 1 to 3, wherein n is 2.
- 10 5. A quinazoline derivative according to any one of claims 1 to 3, wherein n is 3.
6. A quinazoline derivative according to any one of the preceding claims, wherein each group  $R^5$  is a halogeno group.
- 15 7. A quinazoline derivative according to any one of the preceding claims, wherein each group  $R^5$  is selected from chloro and fluoro.
8. A quinazoline derivative according to any one of the preceding claims, which includes  
20 a group  $R^5$  positioned at an ortho- (2-) position on the benzene ring to which it is attached.
9. A quinazoline derivative according to claim 8, wherein the group  $R^5$  positioned at the ortho- (2-) position is fluoro.
- 25 10. A quinazoline derivative according to any one of the preceding claims, wherein in the Formula I, the group of sub-formula (i):



is a group of sub-formula (ii):

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(ii)

wherein (a) one of  $R^{10}$  or  $R^{12}$  is hydrogen and the other is halogeno, and  $R^{11}$  is halogeno, or (b)  $R^{10}$  is halogeno,  $R^{11}$  is halogeno and  $R^{12}$  is selected from hydrogen or halogeno, or (c)  $R^{10}$  is fluoro,  $R^{11}$  is chloro, and  $R^{12}$  is selected hydrogen or fluoro.

5

11. A quinazoline derivative according to claim 10, wherein one of  $R^{10}$  or  $R^{12}$  is hydrogen and the other is fluoro, and  $R^{11}$  is chloro.

12. A quinazoline derivative according to claim 10, wherein  $R^{10}$  is fluoro,  $R^{11}$  is chloro,  
10 and  $R^{12}$  is hydrogen.

13. A quinazoline derivative according to claim 10, wherein  $R^{10}$  is fluoro,  $R^{11}$  is chloro, and  $R^{12}$  is fluoro.

15 14. A quinazoline derivative according to any one of the preceding claims, wherein  $X^1$  is oxygen.

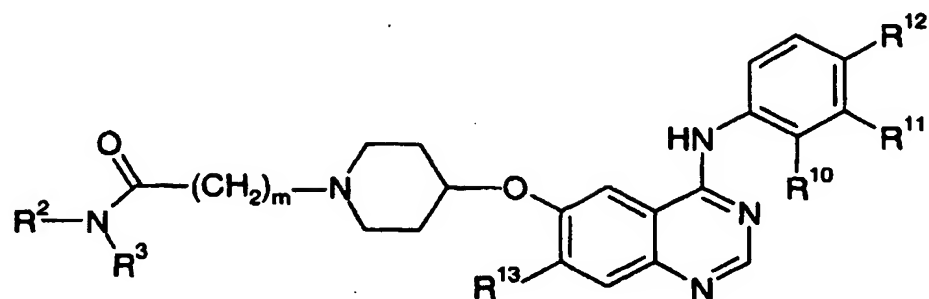
15. A quinazoline derivative according to any one of the preceding claims, wherein  $R^1$  is selected from hydrogen, (1-6C)alkyl and (1-6C)alkoxy(1-6C)alkyl, wherein any (1-6C)alkyl  
20 group in  $R^1$  optionally bears one or more hydroxy or halogeno substituents

16. A quinazoline derivative according to claim 15, wherein  $R^1$  is selected from (1-6C)alkyl, which optionally bears one or more hydroxy or halogeno substituents.

25 17. A quinazoline derivative according to any one of the claims 1 to 13, wherein  $R^1-X^1-$  is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

18. A quinazoline derivative according to claim 17, wherein  $R^1-X^1-$  is methoxy.

19. A quinazoline derivative according to claim 1 of Formula IA:

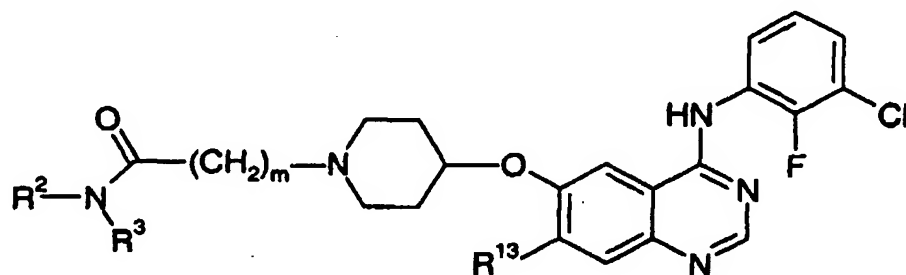


IA

wherein  $R^2$ ,  $R^3$  and  $m$  are as defined in claim 1,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are as defined in any one of claims 10 to 13, and  $R^{13}$  is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

5

20. A quinazoline derivative according to claim 1 of Formula IB:

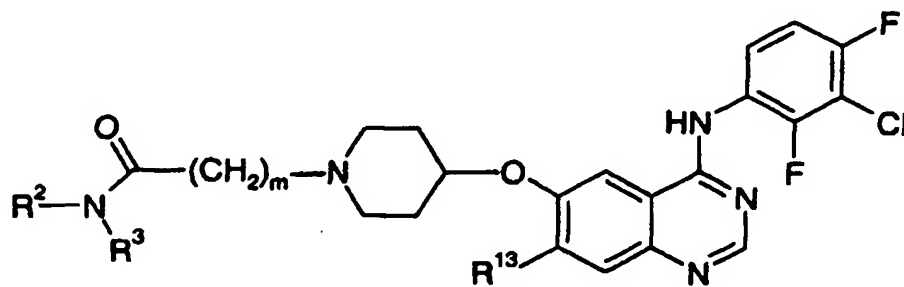


IB

wherein  $R^2$ ,  $R^3$  and  $m$  are as defined in claim 1 and  $R^{13}$  is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

10

21. A quinazoline derivative according to claim 1 of Formula IC:



IC

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wherein  $R^2$ ,  $R^3$  and  $m$  are as defined in claim 1 and  $R^{13}$  is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

22. A quinazoline derivative according to any one of claims 19 to 21, wherein  $R^{13}$  is  
5 methoxy.

23. A quinazoline derivative according to any one of the preceding claims, wherein  $m$  is 0  
or 1.

10 24. A quinazoline derivative according to any one of the preceding claims, wherein  $m$  is 1.

25. A quinazoline derivative according to any one of the preceding claims, wherein  $R^2$  is  
hydrogen or (1-3C)alkyl.

15 26. A quinazoline derivative according to any one of the preceding claims, wherein  $R^2$  is  
hydrogen or methyl.

27. A quinazoline derivative according to any one of the preceding claims, wherein  $R^2$  is  
hydrogen.  
20

28. A quinazoline derivative according to any one of the preceding claims, wherein  $R^3$  is  
(1-6C)alkyl.

29. A quinazoline derivative according to any one of the preceding claims, wherein  $R^3$  is  
25 (1-3C)alkyl.

30. A quinazoline derivative according to any one of the preceding claims, wherein  $R^3$  is  
methyl.

30 31. A quinazoline derivative according to claim 1, which is selected from one or more of  
the following:

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[[1-(N-methylcarbamoylmethyl)piperidin-4-yl]-  
oxy}quinazoline;

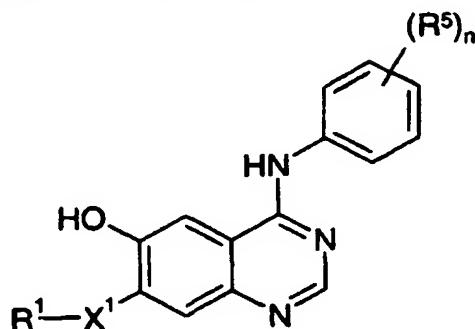
- 4-(3-chloro-2-fluoroanilino)-6-{{1-(N,N-dimethylcarbamoylmethyl)piperidin-4-yl}oxy}-7-methoxyquinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(morpholin-4-ylcarbonylmethyl)piperidin-4-yl}oxy}-quinazoline;
- 5 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(pyrrolidin-1-ylcarbonyl)piperidin-4-yl}oxy}quinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoyl)piperidin-4-yl}oxy}quinazoline;
- 4-(3-chloro-2-fluoroanilino)-6-{{1-(N-(2-dimethylaminoethyl)carbamoyl)piperidin-4-yl}oxy}-
- 10 7-methoxyquinazoline;
- 4-(3-chloro-2-fluoroanilino)-6-{{1-(N,N-dimethylcarbamoyl)piperidin-4-yl}oxy}7-methoxy-quinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(morpholin-4-ylcarbonyl)piperidin-4-yl}oxy}quinazoline;
- 15 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-[2-pyrrolidin-1-ylethyl]carbamoyl)piperidin-4-yl}oxy}quinazoline;
- 4-(3-chloro-2,4-difluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline;
- 4-(3-chloro-2-fluoroanilino)-6-{{1-(N-ethylcarbamoylmethyl)piperidin-4-yl}oxy}-7-
- 20 methoxyquinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-[2-(pyrrolidin-1-yl)ethyl]carbamoylmethyl)piperidin-4-yl}oxy}quinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-(2-methoxyethyl)carbamoylmethyl)piperidin-4-yl}oxy}quinazoline;
- 25 4-(3-chloro-2-fluoroanilino)-6-{{1-(N-(2-dimethylaminoethyl)carbamoylmethyl)piperidin-4-yl}oxy}-7-methoxyquinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]piperidin-4-yl}oxy}quinazoline;
- 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-[2-(piperazin-1-yl)-2-oxoethyl]piperidin-4-
- 30 yl}oxy}quinazoline; and
- 4-(3-chloro-2,4-difluoroanilino)-7-methoxy-6-{{1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]piperidin-4-yl}oxy}quinazoline;
- or a pharmaceutically acceptable salt thereof.



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32. A process for preparing a quinazoline derivative according to any one of the preceding claims, which comprises either

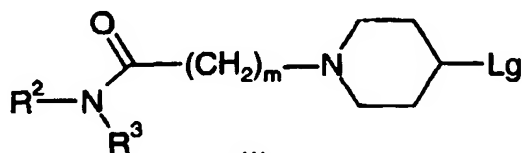
**Process (a)** reacting a compound of the Formula II:



II

5 wherein R¹, X¹, R⁵ and n have any of the meanings defined in claim 1 except that any functional group is protected if necessary,

with a compound of the Formula III:



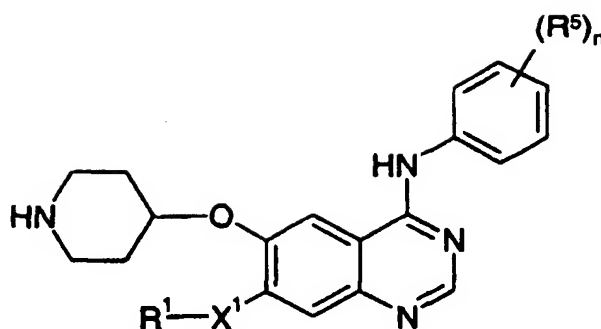
III

10 wherein R², R³ and m have any of the meanings defined in claim 1 except that any functional group is protected if necessary and Lg is a displaceable group, wherein the reaction is conveniently performed in the presence of a suitable base,

**Process (b)** modifying a substituent in or introducing a substituent into another quinazoline derivative of Formula I or a pharmaceutically acceptable salt thereof, as hereinbefore defined except that any functional group is protected if necessary;

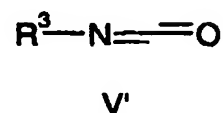
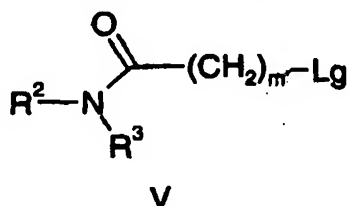
15 **Process (c)** reacting a compound of Formula IV:

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IV

where  $R^1$ ,  $X^1$ ,  $R^5$  and  $n$  are as defined in relation to Formula I except that any functional group is protected if necessary, with a compound of the Formula V or V':



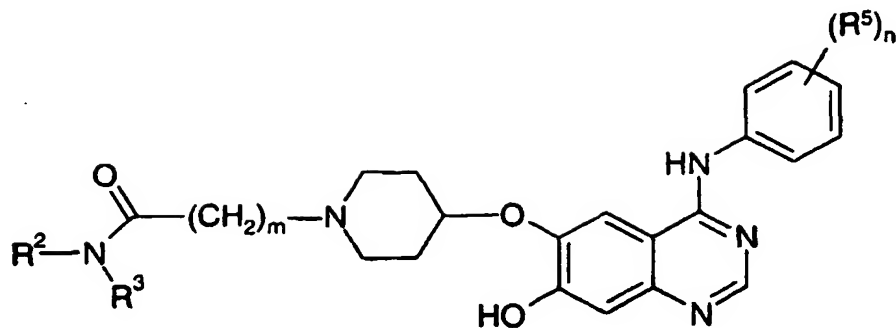
5 wherein  $R^2$  and  $R^3$  are as defined above and  $m'$  is 0, 1, 2 or 3, provided that it is not 0 when  $R^2$  is hydrogen, and Lg is a displaceable group;

**Process (d)** removal of a protecting group from a quinazoline derivative of Formula I, or a pharmaceutically acceptable salt thereof;

**Process (e)** reacting a compound of the Formula II as hereinbefore defined with a  
10 compound of the Formula III as defined hereinbefore except Lg is OH under Mitsunobu conditions;

**Process (f)** for the preparation of those compounds of the Formula I wherein  $R^1-X^1$  is a hydroxy group, cleavage of a quinazoline derivative of the Formula I wherein  $R^1-X^1$  is a (1-6C)alkoxy group;

15 **Process (g)** for the preparation of those compounds of the Formula I wherein  $X^1$  is O and  $R^1$  is not hydrogen, by the reaction of a compound of the Formula VI:

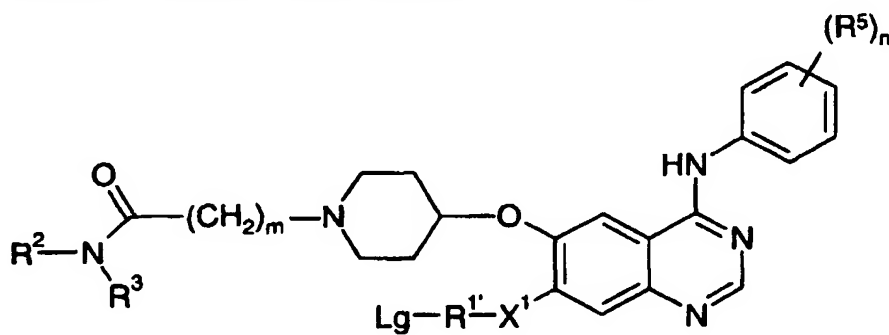


VI

wherein  $R^2$ ,  $R^3$ ,  $R^5$ ,  $m$  and  $n$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a compound of the formula  $R^1$ -Lg, wherein  $R^1$  has any of the meanings defined in claim 1 except that it is not hydrogen and except that any functional group is protected if necessary and Lg is a displaceable group;

**Process (h)** for the preparation of those compounds of the Formula I wherein  $R^1$  contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, alkylation of a quinazoline derivative of the Formula I wherein or  $R^1$  contains a hydroxy group or a primary or secondary amino group as appropriate;

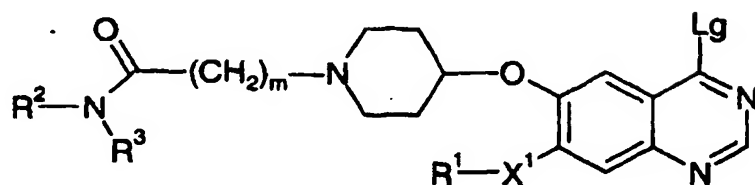
10 **Process (i)** for the preparation of those compounds of the Formula I wherein  $R^1$  is substituted by a group T, wherein T is selected from (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino, (1-6C)alkylthio, (1-6C)alkylsulfinyl and (1-6C)alkylsulfonyl, the reaction of a compound of the Formula VII:



VII

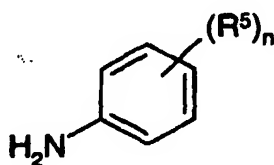
15 wherein  $R^2$ ,  $R^3$ ,  $R^5$ ,  $X^1$ ,  $n$  and  $m$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary,  $R^{1'}$  is a group  $R^1$  as defined herein except that any T groups are replaced with Lg, and Lg is a displaceable group (for example chloro or bromo) with a compound of the formula TH, wherein T is as defined above except that any functional group is protected if necessary;

**Process (j)** reacting a compound of the Formula VIII:



VIII

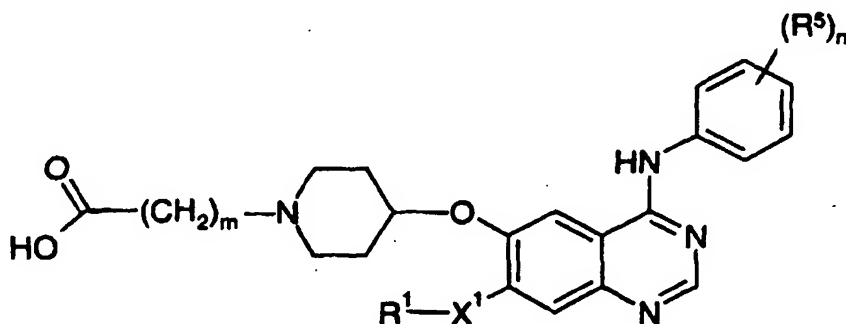
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $X^1$ , and  $m$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary and Lg is a displaceable group as hereinbefore defined,  
 5 with an aniline of the Formula IX:



IX

wherein  $R^5$  and  $n$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, and wherein the reaction is conveniently performed in the  
 10 presence of a suitable acid;

**Process (k)** for the preparation of those compounds of the Formula I wherein  $m$  is 1, 2 or 3, coupling of a compound of Formula X:

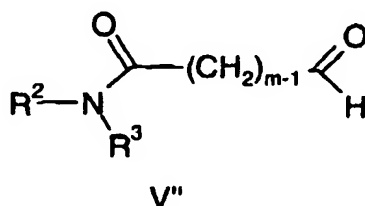


X

wherein  $m$  is 1, 2 or 3 and  $R^1$ ,  $X^1$ ,  $R^5$ , and  $n$  are as hereinbefore defined in claim 1, except  
 15 any functional group is protected if necessary, with a primary or secondary amine of formula  $R^2NHR^3$  where  $R^2$  and  $R^3$  are as defined in claim 1;

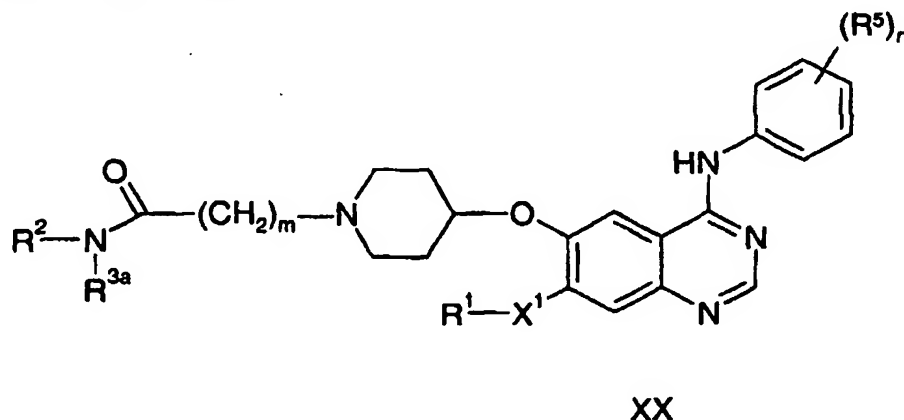
- 79 -

**Process (l)** By reacting a compound of Formula IV as defined above except that any functional group is protected if necessary, with a compound of the Formula V'':



using a reductive amination procedure,

- 5 **Process (m)** for the preparation of those compounds of the Formula I wherein R<sup>3</sup> is (2-6C)alkyl substituted on a carbon atom by an amino, (1-6C)alkylamino, di-(1-6C)alkylamino or a saturated 5 or 6 membered heterocyclic ring which contains NR<sup>8</sup> where R<sup>8</sup> is as defined in claim 1, by reacting a compound of the Formula XX:



- 10 wherein R<sup>3a</sup> is Lg-(2-6C)alkyl, wherein Lg is a displaceable group and wherein R<sup>1</sup>, R<sup>2</sup>, X<sup>1</sup>, R<sup>5</sup>, m and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary,  
with ammonia or with a suitable primary or secondary amine,  
and whereafter any of said processes, any protecting group that is present is removed.

15

33. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in any one of claims 1 to 31 in association with a pharmaceutically-acceptable diluent or carrier.
- 20 34. A quinazoline derivative of the Formula I as defined in any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, for use as a medicament.

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35. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in any one of claims 1 to 31 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal.
- 5 36. A method for producing an anti-proliferative effect in a warm-blooded animal in need of such treatment which comprises administering to said animal a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, as defined any one of claims 1 to 31.
- 10 37. A compound of the Formula VI, VII, VIII, X or XX as defined in claim 32 or a salt thereof.